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REMARKS

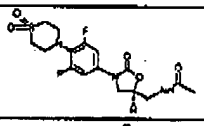
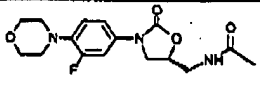
A. Claim Amendments

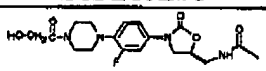
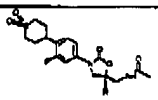
Claims 1, 3-22, and 24-29 are pending in the application, claims 2 and 23 having been canceled in response to a previous Office Action.

Applicants propose to amend claims 1 and 21, as described herein above, to add the term "wherein the oxazolidinone antibacterial drug is no more than sparingly soluble in water" to each claim. Oxazolidinone antibacterial drugs of the formula of claims 1 and 21 are inherently no more than sparingly soluble in water. Some oxazolidinone drugs are only slightly soluble, or even very slightly soluble in water. Each of these descriptive terms relating to solubility is clearly defined by the USP, and understood by those of skill in the art of the present invention. (See solubility table in attached copy of p. 7 of USP XX). Specifically, the term "sparingly soluble" is defined by the USP as referring to a solute that requires from 30 to 100 parts of solvent to be solubilized. It follows that a drug which is only sparingly soluble in water would have a solubility of from 9.9 mg/ml to 32 mg/ml.

Applicants respectfully submit that the amendment of claims 1 and 21 to add the additional solubility term cited immediately above would not add new matter to the present application, as the solubility of the oxazolidinone antibacterial drug element of the present invention in water is an inherent property of the element. As evidence of this inherent property, Applicants present solubility data for four oxazolidinones antibacterial drugs of the formula of claims 1 and 21 in Table I, below.

TABLE 1

Compound	Structure	Solubility in Water (mg/ml)
Oxazolidinone A, Reg. No. 383199-88-0		0.40
Oxazolidinone B (Linezolid)		2.7

Compound	Structure	Solubility in Water (mg/ml)
Oxazolidinone C, Reg.No.383199-88-0		10
Oxazolidinone D, PNU-141659		0.4

The data presented in Table I, above, came from experiments performed by scientists at Pharmacia & Upjohn Company. The data has not been published.

Note that, using the USP standard nomenclature to describe solubility, the oxazolidinone antibacterial drug listed in Table I with the highest solubility, Oxazolidinone C, is only sparingly soluble in water. Linezolid would be considered slightly soluble in water, at about 2.7 mg/ml. The two oxazolidinones with the lowest solubility in water, Oxazolidinones A and D, are only very slightly soluble therein.

For reasons set forth above, Applicants respectfully submit that incorporation of the amendments to claims 1 and 21 proposed herein above would not constitute the addition of new matter to the present application.

B. Status of Previous Grounds of Rejection

Under 37 CFR § 1.113(b), an examiner is required, in any final rejection or action to "repeat or state all grounds of rejection then considered applicable to the claims of the application, clearly stating the reasons in support thereof." (See also, MPEP 706.07).

Several grounds for rejecting claims 1-29 were set forth the previous Office Action on the merits, mailed December 18, 2002. The present Office Action stated that a Declaration under 37 CFR 1.132 filed in response to that Office Action is "insufficient to overcome the rejection of claims 1-29 based upon specific references under 35 USC 102 and 103 as set forth in the last Office action." (Office Action, p. 5, paragraph No. 4) The present Office action goes on to state that arguments set forth in the response to the same Office Action filed with the Declaration "have been considered but are moot in view of the new ground(s) of rejection." (Office Action, p. 5, paragraph No. 5). However, none

of the previous grounds of rejection are repeated in the present Office Action, or otherwise indicated as remaining applicable.

Applicants understand the statement from paragraph No. 5 in the present Office Action, regarding the arguments set forth in response to the previous Office Action being moot, indicate that the previously stated grounds of rejection have been withdrawn, particularly. Specifically, Applicants understand the last statement and the absence of any restatement of the previous rejections with reasons in support thereof, as required under 37 CFR §1.113, to mean that the three rejections of various claims of the present application under 35 U.S.C. §102(b), for anticipation by each of three different references, Maillard (US Pat No. 3,721,675), Borgulya *et al.* (US Pat No. 5,574,055), and Kaplan *et al.* (U.S. Pat. No. 4,727,070) were withdrawn in view of Applicants' amendment and response to the previous Office Action. Applicants similarly understand this last statement, and the absence of statements required under 35 CFR §1.113, to imply that the rejection in the previous Office Action of claims 1-29, under 35 U.S.C. §103(a) over Malliard *et* al, Borgulya *et al.*, and Kaplan *et al.*, in view of Barbachyn *et al.* (U.S. Pat. No. 5,699,792), **Linezolid** (*Drugs of the Future* **1996**, 21(1): 116-1123, XP 000654643) and Miyauchi (U.S. Pat. No. 4,900,730) has also been withdrawn in view of Applicants' response to the previous Office Action on the merits.

C. New Ground for Rejection, Under 35 U.S.C. §103

Claims 1, 3-22, and 24-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over a new combination of three references cited in the previous Office Action, Barbachyn *et al.*, Borgulya *et al.*, Kaplan *et al.*, and Miyauchi.

As was noted in response to the previous Office Action, in order for any claim to be unpatentable over one or more prior art references, under 35 U.S.C. § 103(a):

> "[A]ll the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)." MPEP 2143.03.

1. References Cited Fail to Teach or Suggest Elements of the Invention

Applicants respectfully submit that at least one element common to all the claims of the present application is neither taught nor suggested by Barbachyn *et al.*, Borgulya *et al.*, Kaplan *et al.*, or Miyauchi *et al.*, or by any combination of the four references.

Barbachyn *et al.* is described in the Final Office Action as disclosing "oxazolidinone antimicrobial compounds having an identical structure to the compounds of the present invention," and for stating that such compounds can be "formulated into capsules, dispersed granules, and similar pharmaceutical dosage forms." (Final Office Action, pp. 2 and 3). It is noted in the Final Office Action, that Barbachyn *et al.* fails to disclose any rectal suppository formulation. However, the Office Action goes on to state that "it would be within the level in the art to modify a capsule for rectal suppository administration."

Rectal suppository capsules, particularly soft suppository-shaped elastic capsules, were known at the time the present invention was made. See, for example, Remington: The Science and Practice of Pharmacy, 20th ed. (pub. by Lippincott Williams & Wilkins, 2000), pp 889 to 890, a copy of which is attached. Such suppository capsules were designed with a "soft, globular, gelatin shell" that could be filled with a carrier medium, such as a liquid or oil, with an active agent dissolved therein. (*Id.*) For a description of one known method of producing liquid-filled soft shell capsules, see Bottom *et al.*, *Journal of Pharmaceutical Sciences* 86(9): 1057-1061 (Sept. 1997), a copy of which is attached.

Applicant submits that, even one of ordinary skill in the art might have been able to make modify the teachings of Barbachyn *et al.* to make a "capsule for rectal suppository administration," as suggested by the Office Action, it would not have been obvious to that individual to make any composition of the present invention, including the rectal capsule of claim 9, or to practice any method of treatment or prevention of the present invention. Even prior to (and after) amendment as proposed herein, the only two independent claims, claims 1 and 21, were directed to or included an element of a "pharmaceutical composition, comprising at least one oxazolidinone antibacterial drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at

least one oxazolidinone is poorly soluble. . ." (Language common to claims 1 and 21, after amendment; emphasis added.) Applicants respectfully submit that Barbachyn *et al.* fails to teach or suggest any pharmaceutical composition, including any rectal capsule dosage form, wherein an oxazolidinone antibacterial drug is present in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the at least one oxazolidinone is poorly soluble. Applicants respectfully submit that this particular element of the present invention missing from Borgulya *et al.* cannot be found in any of the other three references cited as basis for this rejection, particularly, when the element is considered after amendment as proposed herein to refer to the inherent properties of solubililty of the oxazolidinone antibacterial drug of claims 1 and 21 in water.

Borgulya *et al.* is cited as disclosing a suppository formulation comprising what the Final Office Action describes as an "oxazolidinone antimicrobial agent" (citing Example A) and formulations of the agent in the form of capsules, dispersed granules, etc. The Final Office Action notes acknowleges that the agent disclosed by Borgulya *et al.* is not one of the same oxazolidinone compounds disclosed by Barbachyn *et al.* The Office Action goes on to state that it would have been obvious to substitute the compound of Barbachyn *et al.* into the composition of Borgulya *et al.* to make the compositions of the present invention.

Borgulya *et al.* teaches a number of different compositions of oxazolidinone derivatives known to be useful in the "prevention of control of depressive, panic and anxiety states, and treatment of certain cognitive disorders and neurodegenerative diseases." (Borgulya *et al.*, Abstract). Example A of Borgulya *et al.* provides a hypothetical example of a suppository of one such derivative, (RS)-3-(4-Cyclohexyl-phenyl_-5-hydroxymethyl-oxazolidin-2-one. However, the Example only describes the suppository in terms of the amount of active ingredient and total suppository mass. No specific information is provided in regarding the composition of the suppository, or regarding the solubility properties of the active agent to be incorporated into the suppository. With such little information provided by Borgulya *et al.* about the one hypothetical suppository disclosed therein, Applicant respectfully submits that Borgulya *et al.* fails to teach or suggest a pharmaceutical composition of any drug in a solid

particulate form dispersed in a pharmaceutically acceptable carrier in which the drug is poorly soluble. The reference also fails to teach or suggest the production of a suppository of any drug which is no more than sparingly soluble in water. Therefore, even if one were to substitute the oxazolidinone antibacterial drug of Barbachyn *et al.* in the compositions of Borgulya *et al.* the two references would not teach or suggest the compositions or methods of the present invention.

The Final Office Action cites Kaplan *et al.* as disclosing a suppository formulation comprising oxazolidinone compounds, where the lipophilic carrier is a hard fat (Example 7). The Final Office Action acknowledges that active agent in Kaplan *et al.* is different from that of the present invention. However, it goes on to state that it would have been obvious to substitute the oxazolidinone antibacterial drugs of Barbachyn *et al.* in the formulation of Kaplan *et al.*. The suppository dosage forms of Example 7 of that reference are described therein as being produced by dissolving a particular antibiotic agent in a hard fat suppository base, and pouring the resulting composition into molds. Like Barbachyn *et al.* and Borgulya *et al.*, Kaplan *et al.* fails to teach or suggest a pharmaceutical composition of any drug in a solid particulate form dispersed in a pharmaceutically acceptable carrier in which the drug is poorly soluble. Like the other two references, Kaplan *et al.* also fails to teach or suggest the production of a suppository of any drug which is no more than sparingly soluble in water. Therefore, Applicants respectfully submit that the pharmaceutical compositions of and methods of the present invention would not have been obvious to one of ordinary skill in the art, even if they were to substitute the oxazolidinone antibacterial drugs of Barbachyn *et al.* in the suppository formulation of Kaplan *et al.*

The final reference cited as basis for the present rejection, Miyauchi, is described in the Final Office Action as disclosing rectal suppositories of antibacterial agents that are "micronized from 1-50 microns, and dissolved in the hard fat Witepsol H-15." Miyauchi teaches that the medicines employed in the formulations disclosed therein are preferably "water-soluble medicines." (Miyauchi, col. 5, lines 26-27). The term "water-soluble" is defined as "a solubility of not more than 30 parts water per one part of substance on the basis of the United States Pharmacoperia." (*Id.*, col. 2, lines 43-46) This definition

clearly takes. As noted in the Amendment remarks section, herein-above, the oxazolidinone antibacterial drug in the compositions and used in the methods of the present invention is no more than "sparingly soluble" in water, on the basis of the same US Pharmacoperia definition standard. In other words, the oxazolidinone antibacterial drug has a solubility of one part drug to more than 30 parts water. This inherent property of the at least one oxazolidinone antibacterial drug of the compositions and method of the present invention is made even more clear upon incorporation of the amendment proposed herein. Miyauchi neither teaches nor suggests that the drug in the micronized particles disclosed in that reference is poorly soluble in the hard fat base used to make the rectal suppositories disclosed therein. Therefore, Miyauchi fails to make up for the deficiencies in the teachings of the other three references cited as basis for this rejection.

2. Missing Elements Not Obvious from General Knowledge of the Art

In order to more clearly emphasize the surprising and unexpected nature of the pharmaceutical compositions and methods of the present invention, Applicants propose to amend the only two independent claims herein by inserting a reference to an inherent property of the oxazolidinone antibacterial drugs of claims 1 and 21, a reference to the fact that those particular drugs are no more than sparingly soluble in water. (proposed amended language underlined). As further evidence of the expectations of one of ordinary skill in the art, Appliclants submit The Theory and Practice of Industrial Pharmacy, ed. by Lachman *et al.* 3rd ed., pub. by Lea & Febiger, Philadelphia (1986), pp 564-567. Beginning on p. 566 of that reference is a discussion of the effect of solubility of a drug in a vehicle and in colon fluids on absorption through the rectal mucosa. It specifically teaches that in order for a drug to be absorbed, it "must be released from the suppository and distributed to sites of absorption." (Lackman *et al.* p. 566). That particular reference constitutes evidence that the general knowledge available to one of ordinary skill in the art at the time the present invention was made taught away from any pharmaceutical composition of a drug for rectal administration wherein the drug is present in particulate form in a carrier, and the drug is no more than sparingly soluble in water. For, if a drug is no more than sparingly soluble in water, one would not expect it to go into solution in colon fluids, so that it can be absorbed through the rectal mucosa.

For reasons set forth above, Applicants respectfully traverse the rejection of claims 1, 3-22, and 24-29, under 35 U.S.C. §103(a) as being unpatentable over Barbachyn *et al.*, Borgulya *et al.*, Kaplan *et al.*, and Miyauchi.

SUMMARY

Applicants respectfully request entry of all amendments proposed herein above, as all would place the application in a better position on appeal, should appeal become necessary. For reasons given above, Applicants respectfully submit that all of the claims remaining pending in the present case (i.e., claims 1, 3-22, and 24-29), after amendment as proposed herein, are in condition for allowance. Issuance of all the claims is, therefore, requested. The Examiner is invited to contact the undersigned at the telephone number given below, should he wish to discuss the present amendment and suggest changes to the claims in order to further prosecution of the application.

Dated: Dec. 11, 2003

Karen B. King
Attorney for Applicants
Reg. No.: 41,898
Phone No.: (734) 622-4837

tion, *Reagents, Indicators, and Solutions*, and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity—Unless otherwise stated, the specific gravity basis is 25°/25°, i.e., the ratio of the weight of a substance in air at 25° to the weight of an equal volume of water at the same temperature.

Temperatures—Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at 25°. Where "controlled room temperature" is specified, a temperature range between 15° and 30° is intended.

Time Limit—In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum—The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury, unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water—Where water is called for in tests and assays, *Purified Water* is to be used. For special kinds of water such as "carbon dioxide–free water," see the introduction to the section, *Reagents, Indicators, and Solutions*.

Water and *Loss on Drying*—Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading *Water*. Where the determination is made by drying under specified conditions, the test is generally given under the heading *Loss on drying*. However, *Loss on drying* is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Description—Information on the "description" pertaining to an article, which is relatively general in nature, is provided in the reference table, *Description and Relative Solubility of USP and NF Articles*, in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of the integrity of an article.

Solubility—The statements concerning solubilities given in the reference table, *Description and Relative Solubility of USP and NF Articles*, for Pharmacopeial articles are not standards or tests for purity, but are provided primarily as information for th se who use, prepare, and dispense drugs and/or related articles. Only where a special, quantitative solubility test is

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 and over

Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers—The *container* is the device that holds the article and that is or may be in direct contact with the article. The *immediate container* is that which is in direct contact with the article at all times. The *closure* is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

Light-resistant Container (see *Light Transmission* under *Containers* ⟨661⟩)—A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents have been used. Where it is directed to "protect from light" in an individual monograph, storage in a light-resistant container is intended.

Well-closed Container—A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container—A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from

The Theory and Practice of Industrial Pharmacy

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19

Suppositories

LARRY J. COBEN *and* HERBERT A. LIEBERMAN

A suppository is a medicated solid dosage form generally intended for use in the rectum, vagina, and to a lesser extent, the urethra. Rectal and urethral suppositories usually employ vehicles that melt or soften at body temperature, whereas vaginal suppositories, sometimes called *pessaries*, are also made as compressed tablets that disintegrate in the body fluids.

Oleum Theobromae was first recommended to American pharmacists by A. B. Taylor in 1852, and it soon grew in popularity as the suppository base of choice. Glycerinated gelatin mixtures did not appear as suppository vehicles until about 1875. In 1913, Bruno Solomon published a critical study of suppository bases, in which he classified them into three broad types: (1) cocoa butter, (2) fat and wax combinations with cocoa butter, and (3) glycerinated gelatin bases.

In the 1930s, several unwanted side effects and disadvantages inherent to oral therapy focused attention, principally in Europe, on the rectal route for administering drugs. Industrial concerns, principally in Germany and France, synthesized special lipid excipients, which were designed to replace cocoa butter. Water-soluble polyethylene glycol type bases were introduced as an improvement on glycerinated gelatin and lipid type suppository bases.

For the combined prescription and over-the-counter market, suppositories represent about 1% of all medications dispensed in the United States. The suppository is a far more popular medication in Europe and South America than in the United States.

Dose Characteristics

Opinion is mixed concerning the amount of drug that should be given rectally as compared with the oral dose. In general, for rectal administration, one-half to two or more times the oral dose is given for all but very potent drugs. The range in dose can be attributed to the availability of the drug from the particular suppository base used. The correct dose for any drug depends on the rate of release of the drug from the suppository. As a consequence, the suppository base and the amount of drug must be considered concomitantly. Since the vehicle can change the rate of drug absorption, the amount of drug to be given in suppository form depends on the vehicle and the chemical and physical form of the drug given.

Rectal suppositories for adults weigh about 2 g and are usually tapered to resemble a torpedo shape. Children's suppositories weigh about 1 g and have a corresponding reduction in size. Vaginal suppositories weigh about 3 to 5.0 g and usually are molded in the globular or oviform shape, or compressed on a tablet press into modified conical shapes. Urethral suppositories, sometimes called *bougies*, are pencil-shaped and pointed at one extremity. Urethral suppositories intended for males weigh about 4 g each and are 100 to 150 mm long; for females, they are 2 g each and usually 60 to 75 mm in length. Figure 19-1 illustrates a representative sampling of several commercially available suppositories.

Therapeutic Uses

Drugs may be administered in suppository form for either local or systemic effects. Such action depends on the nature of the drug, its concentration, and the rate of absorption. Emollients, astringents, antibacterial agents, hormones, steroids, and local anesthetics are dispensed in suppository form for treating local conditions of either the vagina, rectum, or urethra.

Many articles have been published recently

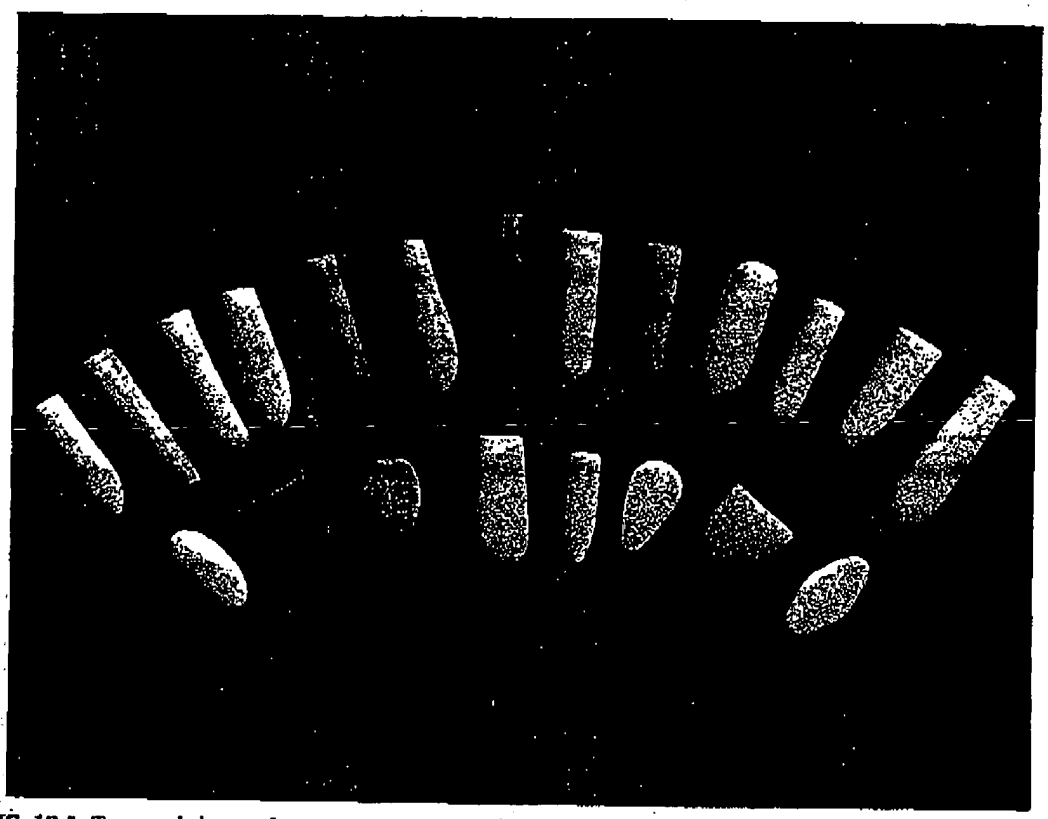

FIG. 19-1. *Types and shapes of suppositories.*

on the use of prostaglandin-containing vaginal suppositories for interruption of early pregnancy.

Rectal suppositories are primarily intended for the treatment of constipation and hemorrhoids. Suppositories are also administered rectally for systemic action. A wide variety of drugs are employed, e.g., analgesics, antispasmodics, sedatives, tranquilizers, and antibacterial agents.

Rectal suppositories are also utilized for systemic actions in conditions where oral medication would not be retained or absorbed properly, such as during severe nausea and vomiting or in paralytic ileus.

Factors Affecting Drug Absorption from Rectal Suppositories

Physiologic Factors

A number of drugs cannot be administered orally, because either the drugs are affected by the digestive juices, or their therapeutic activity is modified by the liver after absorption. After a drug is absorbed from the small intestine, the drug is carried by the hepatic portal vein to the liver. The liver modifies many drugs chemically and thereby often reduces their systemic effectiveness. On the other hand, a major portion of the same drugs can be absorbed from the anorectal area and still retain therapeutic values. The lower hemorrhoidal veins surrounding the colon and rectum enter into the inferior vena cava and thus bypass the liver. The upper hemorrhoidal vein does connect with the portal veins leading to the liver. More than half (50 to 70%) of rectally administered drugs were reported absorbed directly into the general circulation.[1] The lymphatic circulation helps also in absorbing a rectally administered drug and in diverting the absorbed drug from the liver.[2]

The pH of the rectal mucosa plays a significant rate-controlling role in drug absorption. Schanker reported that the rat colon has a pH of approximately 6.8, a pH slightly more acidic than previously believed.[3] Rectal fluids have vir-

tually no buffer capacity, and as a consequence, th dissolving drugs determine the pH existing in the anorectal area. Schanker states that weaker acids and bases are more readily absorbed than the stronger, highly ionized ones. These findings suggest that the barrier separating the colonic lumen from the blood is preferentially permeable to the un-ionized forms of drugs. Thus, the absorption of a drug would be enhanced most likely by a change in the pH of the rectal mucosa that would increase the proportion of un-ionized drug. The effect of intraluminal pH on the absorption of several acidic and basic drugs is shown in Table 19-1.

As shown in Table 19-1, absorption of acidic drugs was markedly increased when the pH of the surrounding fluids was lowered. The absorption of salicylic acid rose from 12% at a pH of approximately 7 to 42% at pH 4. In contrast, with a basic drug like quinine, which becomes more ionized at the lower pH values, absorption was decreased from 20% at pH 7 to 9% at pH 4. Phenol is a weak acid and is almost completely un-ionized at both pH 7 and pH 4. Consequently, there was little change in absorption when the pH was lowered.

Riegelman and Crowell have demonstrated that one of the rate-limiting steps in drugs absorption is the diffusion of the drug to the site on the rectal mucosa at which absorption occurs. This diffusivity is influenced not only by the nature of the medicament, such as the presence of surfactant or the water-lipoidal solubility of the drug, but also by the physiologic state of the colon, that is, the amount and chemical nature of the fluids and solids present.

The state of the anorectal membrane also plays a role in drug absorption.[4] This membranous wall is covered with a relatively continuous mucous blanket, which can act as a mechanical barrier for the free passage of drug through the pore space where absorption occurs.

Drugs absorbed from the small and large intestines would most likely be absorbed from the anorectal area. The similarity in the patterns of drug absorption from the small and large intestines makes it unlikely that a drug that has passed through the small intestine would be significantly absorbed from the colon.[5] Conversely, a drug that can be absorbed from the colon most likely would have been completely absorbed in the small intestine before reaching the colon.

It should be recognized that although average body temperature is 37°C, patient temperatures may vary from 36 to 38°C, owing to daily and monthly cycles. The suppository formulator must bear in mind the lower limit as a "worst case."

TABLE 19-1. *Effect of Intraluminal pH on Absorption from the Rat Colon*

		pH of the Perfusion Solution	
Drug	*pKa*	*6.8–7.2**	*3.6–4.0†*
Acid		% Absorbed	% Absorbed
Salicylic	3.0	12	42 ± 3
Benzoic	4.2	19	50 ± 7
Phenol	9.9	36	37 ± 1
Base			
Aniline	4.6	44	32 ± 5
Quinine	8.4	20	9 ± 1

*The solution, which entered the colon with a pH of 7.2 and left with a pH of 6.8, is a weakly buffered saline solution.

†This highly buffered solution entered the colon with a pH of 3.6 and left with a pH of 4.0.

Physicochemical Characteristics of the Drug

The sequence of events leading to drug absorption from the anorectal area can be diagramatically represented as follows:

Drug in vehicle ⟶ Drug in colon fluids ⟶ Absorption through the rectal mucosa

In order for the drug to be available for absorption, it must be released from the suppository and distributed by the surrounding fluids to sites of absorption. By dissolving in the fluids, there is wide contact of the drug with the lumen walls, thereby increasing drug contact with a large number of absorption sites. If the drug has a lipid-water coefficient favoring fat solubility, the drug is released slowly from its suppository excipient. Allawala and Riegelman report that a drug that is very soluble in cocoa butter and present in low concentration does not escape to the surrounding aqueous solution as readily as the drug that is slightly soluble in the cocoa butter vehicle and present at levels at or close to saturation.[6] Thus, water-soluble, oil-insoluble salts are preferred in fat-base suppositories. For water-soluble suppository type bases, from which the drug is released as the vehicle dissolves, the water-soluble type salt is the one of choice for quicker drug absorption. For example, to increase the absorption rate from suppositories, ephedrine sulfate and quinine hydrochloride, as well as sodium barbital and sodium salicylate, are preferred to their corresponding bases and acids.

The rate-limiting step in drug absorption from suppositories is the partitioning of the dissolved drug from the melted base and not the rate of solution of the drug in the body fluids. Riegelman and Crowell hav shown that the rate at which the drug diffuses to the surface of the suppository, the particle size of the suspended drug, and the presence of surface-active agents are factors that affect drug release from suppositories.[4] Solution of the drugs in solid polyethylene glycol and oleaginous bases resulted in prolonged absorption times, because the drug is slowly eluted into the surrounding fluids. As would be expected, the larger the particle size, the slower the rate of solution, and as a consequence, the drug absorption rate is decreased with an increase in drug particle size. Surfactants can both increase and decrease drug absorption rate. For instance, in the case of sodium iodide, absorption is accelerated in the presence of surfactants and appears to be proportional to the relative surface tension lowering of the vehicle. In addition, Riegelman and Crowell state that the acceleration of sodium iodide absorption might also be attributed to the mucus-peptizing action of the vehicle.[4] The rectal membrane is covered by a continuous mucous blanket, which may be more readily washed away by colonic fluids that have reduced surface tension. The cleansing action caused by the surfactant-containing vehicle may make additional pore spaces available for drug absorption, thus facilitating drug movement across the rectal membrane barrier. In the case of phenol-type drugs, absorption rate is decreased in the presence of surfactant, probably because of the formation of a drug-surfactant complex.

Schanker showed that the absorption of several acid and base compounds in solution, as in a retention enema, was not affected over a 10-fold range of concentration. In the case of the retention enema, the absolute amount of drug absorbed was directly proportional to the initial saturation concentration present and not to any excess beyond this amount. If the luminal concentration of drug is above a particular amount, which varies with the drug, the rate of absorption does not change with further increases in drug. Thus, colonic absorption of drugs is a matter of simple diffusion across the colonic membrane. In suppositories, however, concentration does play a role in determining the rate of release of the drug from suppository bases.

Once the drug is released from the suppository base and reaches the site of absorption on the lumen wall, the lipid-soluble undissociated drug is the most readily absorbed form. Completely ionized drugs like quaternary ammonium compounds and sulfonic acid derivatives are poorly absorbed. Un-ionized substances that are lipid-insoluble also are poorly absorbed.[3]

The relation between the degree of ionization and the rate of absorption of drugs is illustrated in Table 19-1. Weak acids with a pKa below 4.3 and weak bases with a pKa below 8.5 are usually readily absorbed.[3] Highly ionized compounds are poorly absorbed. Acids having pKa values below 3.0 and pKa values for bases above 10.0 (quaternary ammonium salts) indicate negligible absorption rates. This relation suggests that the anorectal and colonic mucosae are selectively permeable to the uncharged drug molecule, whereas the ionized drugs penetrate the mucosa poorly or negligibly. Thus, drug absorption can be increased by the use of buffer solutions or salts that convert the pH of the anorectal area to a value that increases the concentration of un-ionized drug.

In summary, absorption of drugs from the anorectal area is affected by such physiologic factors as colonic contents, circulation, pH, lack of buffering capacity, physiologic state, and the mucous blanket on the lumen wall. The physicochemical characteristics of drugs affecting absorption are the lipid/water partition coefficient and the degree of ionization. When the amount of drug in the rectal fluids is above the rate-determining level, marked increases in drug concentration play no role in altering established drug absorption rates. Drug concentration is related, however, to release rates from suppository bases. The presence of surfactant may or may not aid absorption, depending on concentration and possible interaction with the drug. Drug particle size is directly related to absorption rate.

Physicochemical Characteristics of the Base and Adjuvants

Various properties of the suppository base can affect drug absorption. Heinmann et al. reported that with use of sodium phenobarbital, the absorption rate is faster from fatty bases having a lower melting range than from those with higher melting ranges.[7] It was also shown that absorption rate increases along with hydroxyl values. Pasich et al.,[6] using polyethylene glycol bases, showed a decrease in absorption time with increase in the molecular mass of the polyethylene glycols (PEGs) used.

Since fatty bases may harden for several months after molding, this rise in melting range certainly would affect absorption (see "Examples of Typical Stability Problems," presented later in this chapter).